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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,245	10/09/2001	Joseph Roberts	078728-0104	3976

22428 7590 03/14/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
03/14/2008	PAPER

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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JOSEPH ROBERTS and NATARAJAN SETHURAMAN

Appeal 2007-3933
Application 09/972,245
Technology Center 1600

Oral Hearing Held: February 12, 2008

Before TONI R. SCHEINER, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

ON BEHALF OF THE APPELLANTS:

SHAUN R. SNADER, ESQUIRE
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The above-entitled matter came on for hearing on Tuesday, February 12, 2008, commencing at 9:40 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia, before Carol A. Lowe, RPR, CCR No. 0313084, Notary Public.

JUDGE SCHEINER: While you're doing that, I would like you to know we have an observer.

MR. SNADER: Sure.

JUDGE SCHEINER: Okay. And whenever you're ready -- take whatever time you need, but then once you get started you'll have 20 minutes.

MR. SNADER: Thank you. If you're ready, I'm ready to get started.

JUDGE SCHEINER: Whenever you are.

MR. SNADER: Good morning. There are six grounds of rejection on appeal, both anticipation and obviousness. Although the references between these grounds for rejection are different, all of the rejections share a common flaw. And that flaw is that the examiner has misconstrued biological activity to encompass measuring immunogenicity or antigenicity.

And, as I will explain, this is not the broadest reasonable interpretation of the claims, because it runs directly contrary to the teachings of the specification and the understanding of one of skill in the art.

To start out I want to talk just briefly about the claim subject matter. Generally the claims are directed to methods of determining how a -- or an active agent can be modified in order to optimize the activity of that therapeutic agent.

More specifically, it's a method for determining the type of biocompatible material, the extent of modification and the conditions for modifications of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of the therapeutic agent.

The background of the specification teaches that modifying a therapeutic agent with a biocompatible polymer is nothing new. That's been done in the past. It's known that it increases the half-life in some cases. And it also can reduce the immunogenicity and antigenicity.

The spec background also teaches that in the past the extent or the type of modification was determined by looking at a couple of things, either the antigenicity and immunogenicity or an acceptable loss of biological activity.

In other words, they modified the agent; determined the loss of biological activity. And if it was within an acceptable range, that was considered an acceptable modification.

Similar with antigenicity and immunogenicity, they looked at the extent to which the modified agent would either stimulate the production of antibodies or would cross-react with antibodies to the unmodified therapeutic agent.

The background of the specification teaches that these types of prior art methods of looking at immunogenicity and antigenicity were flawed. They were not sufficient. Using these methods it wasn't possible to predict the optimal type of modification.

The inventors discovered a scheme or a method to assess the modification of the biological -- or the therapeutic agent that avoided the problems with limiting what you're looking at to immunogenicity and antigenicity.

JUDGE SCHEINER: Excuse me. How was loss of biological activity determined? You know, where you talk about acceptable -- one of the criterion -- criteria --

MR. SNADER: Yes.

JUDGE SCHEINER: -- was loss, acceptable loss of biological activity, how was that --

MR. SNADER: Well, to a certain extent it depends on the biological activity. I believe one of the prior art references -- I think it's the Chinol reference -- it modified the biological agent and then used a binding assay to determine how the modified compared with the unmodified.

And I think in that case it was avidin -- the modified agent was an avidin or a variation of avidin. And the binding assay was a biotin binding assay.

JUDGE SCHEINER: Okay.

MR. SNADER: Key to that is the fact that the loss of acceptable binding activity was determined before the agent is administered to the subject.

JUDGE SCHEINER: Okay.

MR. SNADER: Now, the claimed method which applicants found to be an improvement over the prior art methods that looked at immunogenicity and antigenicity administers the biological agent and then after it's administered to the subject looks at the biological -- biological activity of that therapeutic agent.

And based on looking at the biological agent after it has been administered and after a booster dose has been given the applicants found that this is a much better predictor of the effectiveness of the modified therapeutic agent as compared to the prior art methods.

And specifically that's demonstrated in example three of the specification where it is shown that measuring immunogenicity and

antigenicity was not as good of a predictor of the usefulness of the modified therapeutic agent as the claimed method.

JUDGE SCHEINER: Okay. Well, why don't we get to what the real issue here is? And that is what you mean by biological activity --

MR. SNADER: Yes.

JUDGE SCHEINER: -- based on the specification.

MR. SNADER: Yes.

JUDGE SCHEINER: And why measuring antigenicity -- apart from what you say the focus of the invention is, how is measuring the antigenicity or immunogenicity after a boost excluded by your specification?

MR. SNADER: Okay. Applicants agree -- and I don't think there's any dispute -- the claims are to be given their broadest reasonable interpretation during prosecution.

And that broadest reasonable interpretation is contained by both the understanding of one of skill in the art and the teachings of the specification. In other words, you can't look at the claims in context. They have to be construed from the perspective of the specification.

Here the specification specifically addresses in the background of the invention section the prior art methods of --

JUDGE FREDMAN: But why would we not look at page 13 where you define biological activity as, for example -- and they say examples of biological activity -- this is at page 13 about lines nine and 10. A molecule binding a receptor or antibody. It seems to me that an antigen binding an antibody is the molecule binding an antibody.

MR. SNADER: You would look at page 13 of the specification. And it is defined there, but you would not look at page 13 in

isolation. You would look at page 13 in the context of the entire specification.

And in the background of the invention section it talks about how measuring immunogenicity and antigenicity, something known in the art -- we're doing something different. We're looking at biological activity.

JUDGE FREDMAN: So you think we should read a limitation from the background section as against an expressed definition on page 13.

MR. SNADER: I don't think you have to read it against. I don't think the two are inconsistent. For example, you talk about in the examples here that antibody binding could be used to measure the biological activity. In some cases that's correct.

For example, if you have a therapeutic agent that's an antibody and you look at that antibody's binding to its receptor, you are looking at its biological activity. That's entirely consistent with this definition as what is meant by these -- this definition examples.

JUDGE FREDMAN: Doesn't every protein essentially have as one of its biological activities the ability to bind a cognate antibody?

MR. SNADER: Each protein has that ability. I don't think that is embraced by biological activity.

And the reason that's not embraced by biological activity is the specification specifically states immunogenicity and antigenicity. This is what these concepts are.

Prior art looked at these to determine the type and extent of modification. We're doing something different. We're not looking at the immunogenicity and antigenicity. We're looking --

JUDGE FREDMAN: But, in fact, you already said that if it

was an antibody that was -- it would be -- you could look at the antigenicity. So you're saying it depends.

MR. SNADER: I'm -- just to be clear, you could look at, depending on -- for example, if the therapeutic agent is an antibody, you --

JUDGE FREDMAN: Or an antigen, let's say.

MR. SNADER: Antigen. You could look at antibody binding as a measure of the biological activity. You're not looking at immunogenicity and antigenicity which are distinct concepts related to how the body reacts in a narrow context to removing these as foreign matter?

So biological activity in some limited circumstances could be looking at antibody binding, but it's the antibody binding that relates to its biological function.

So, for example, in the Chinol reference it does -- it is a -- it is directed to a pegylated avidin. I think streptavidin. They look at biotin binding before it's administered to a subject to determine the acceptable loss. And they do that with a biotin binding assay. They look at the biological activity.

However, once it's administered they no longer look at the biological activity. They look at the antibody binding to that pegylated avidin. And that is consistent with the general prior art teachings that you look at antigenicity and immunogenicity, but you don't look at the biological activity.

Once it was administered they didn't bother to look at its ability to continue binding biotin after a booster dose. They simply looked at its loss of biological activity in vitro beforehand, saw that it could still bind biotin, administered it and then focused on the immunogenicity and

antigenicity consistent with the prior art.

So I guess to answer your question, biological activity in some limited circumstances can be binding to an antibody if that is the biological effect of the therapeutic agent.

But in general simply looking at antibody binding is not looking at biological activity. It's consistent with the prior art that was distinguished which is looking at the antigenicity and immunogenicity.

JUDGE GRIMES: In the case of an antibody that's a therapeutic agent under your definition the specific binding of that antibody to its antigen would be its biological activity whereas its effect of raising other antibodies to itself would be antigenicity or immunogenicity?

MR. SNADER: Correct. Correct. And just to be clear, there are specific definitions of antigenicity and immunogenicity provided in the specification; page 1, 21 to 23.

And that's absolutely correct; that in that case a way of looking at biological activity would look at the binding to the antigen. It would not involve looking at antibodies that were raised to that antibody.

And I'd like to talk just briefly about each of the references and why they do not encompass biological activity. Generally speaking I think we've already covered the fact that biological activity does not encompass this concept of looking at immunogenicity and antigenicity.

And for that reason none of these references teach or suggest the claimed method. More specifically, we've already talked a little bit about the Chinol reference. It did not look at its biotin bind -- the pegylated avidins, biotin binding activity after it was administered.

Acceptable loss was determined before it was administered.

And then it was simply looking at the antibodies raised to the pegylated avidin.

Similarly, the Decker reference uses two different pegylated therapeutic agents. And they were looking at the immunogenicity of these pegylated agents as discussed on page 384, second column under results.

Now, they did look at biological binding; but, again, they did that -- looked at it before being administered to determine the extent of -- excuse me. Determine the acceptable loss of binding activity.

The Alvarez reference and remaining 103 references are even more distant from the claimed invention. Alvarez is just looking at a single pegylated agent and determining its toxicity, specifically the incidence of pancreatitis in patients treated with pegylated asparaginase as compared to native asparaginase.

There is no measurement of biological activity after its administration. There's no discussion of modifying the pegylation. It's simply looking at the incidence of pancreatitis in a clinical setting.

Graham is very similar in its teachings in that it doesn't look at the biological activity after administration. It's concerned with the toxicity of these agents after administration. And toxicity of the biological -- of the pegylated active agent is something known in the art and a problem that people have attempted to address by modifying the types and extent of modification.

Francis, again, looking at immunogenicity, not biological activity; does not assay the biological activity after administration.

The remaining references are generally used to show specific features of depending claims. For example, Petersen is cited to show only

specific polyethylene glycols.

That's not properly combinable with the other references for the same reason -- is that all of these references even in combination lack a teaching that biological activity should be assayed after administration to a patient and after a booster dose is provided.

JUDGE SCHEINER: Do you have anything further?

MR. SNADER: I have nothing further. I'd be happy to --

JUDGE SCHEINER: Okay. I think we understand the issue.

MR. SNADER: Okay. Thank you very much.

JUDGE SCHEINER: Thank you.

(Whereupon, the proceedings at 9:54 a.m. were concluded.)